Pharmacoinformatics for Drug Discovery

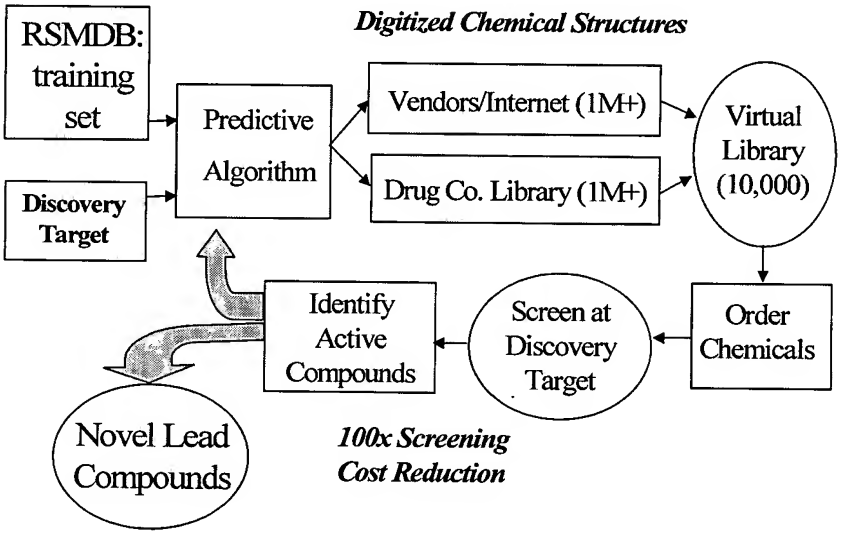


FIG. 1

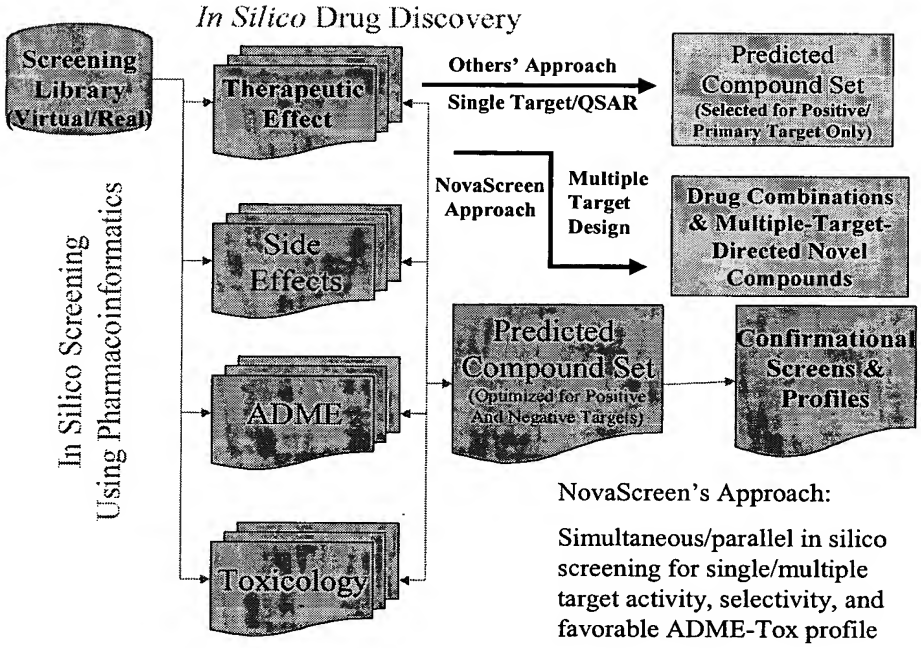

In Silico Drug Discovery
Screening Library (Virtual/Real)
Therapeutic Effect
Side Effects
ADME
Toxicology
In Silico Screening Using Pharmacoinformatics
Others' Approach
Single Target/QSAR
Predicted Compound Set (Selected for Positive/ Primary Target Only)
NovaScreen Approach
Multiple Target Design
Drug Combinations & Multiple-Target-Directed Novel Compounds
Predicted Compound Set (Optimized for Positive And Negative Target(s))
Confirmational Screens & Profiles
NovaScreen's Approach:
Simultaneous/parallel in silico screening for single/multiple target activity, selectivity, and favorable ADME-Tox profile

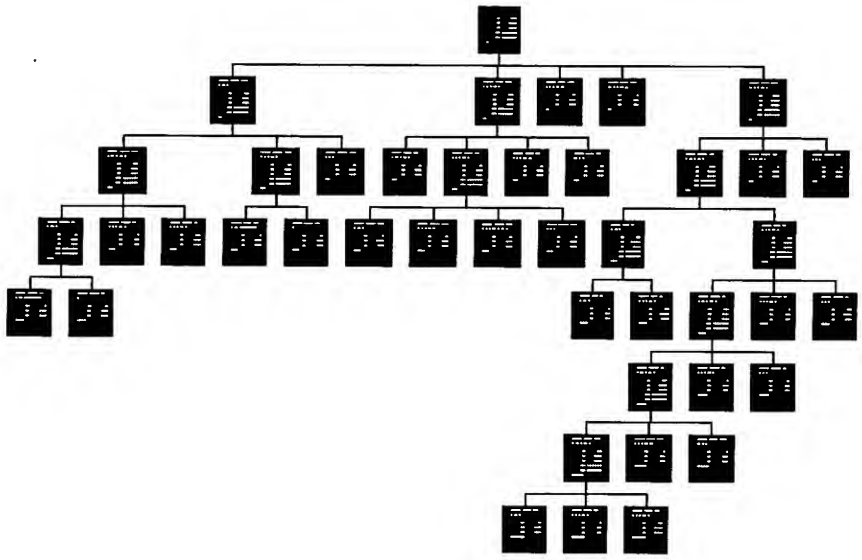
FIG. 2

$$\sum P_T = \sum P_D - \sum P_{UD}$$

$$\sum P_D = \sum P_{prot\_1} + \sum P_{prot\_2} + \sum P_{prot\_n} + \cdots + \sum P_{phys\_1} + \sum P_{phys\_2} + \sum P_{phys\_n} \cdots$$

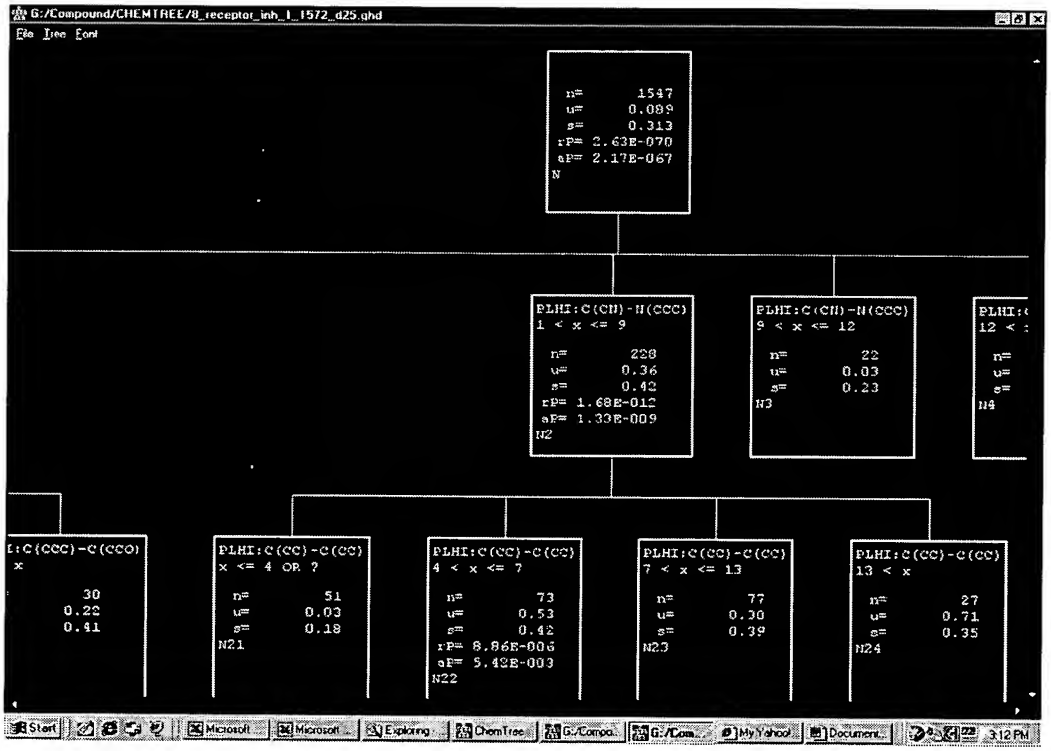
$$\sum P_{UD} = \sum P_{prot\_1_u} + \sum P_{prot\_2_u} + \sum P_{prot\_n_u} + \cdots + \sum P_{phys\_1_u} + \sum P_{phys\_2_u} + \sum P_{phys\_n_u} \cdots$$

FIG. 3



400

FIG. 4


G:/Compound/CHEMTREE/8_receptor_inh_I_1572_d25.ghd
File Tree Font
n= 1547
u= 0.089
s= 0.313
rP= 2.63E-070
aP= 2.17E-067
N
PLHI:C(CN)-N(CCC)
1 < x <= 9
n= 228
u= 0.36
s= 0.42
rP= 1.68E-012
aP= 1.33E-009
N2
PLHI:C(CN)-N(CCC)
9 < x <= 12
n= 22
u= 0.03
s= 0.23
N3
PLHI:C(CC)-C(CC)
x <= 4 OR ?
n= 51
u= 0.03
s= 0.18
N21
PLHI:C(CC)-C(CC)
4 < x <= 7
n= 73
u= 0.53
s= 0.42
rP= 8.86E-006
aP= 5.42E-003
N22
PLHI:C(CC)-C(CC)
7 < x <= 13
n= 77
u= 0.30
s= 0.39
N23
PLHI:C(CC)-C(CC)
13 < x
n= 27
u= 0.71
s= 0.35
N24
Start
3:12 PM

500

FIG. 5

- PLHI: N(CC) - N(CC) X = 3
  - PLLO: C(CCC) - N(CC) X = 2
  - PLHI: C(CCC) - N(CC) X = 5
  - PLLO: C(CNN) - N(CC) X = 1
  - PLHI: C(CNN) - N(CC) X = 2

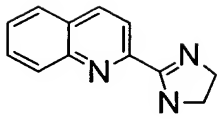


FIG. 6

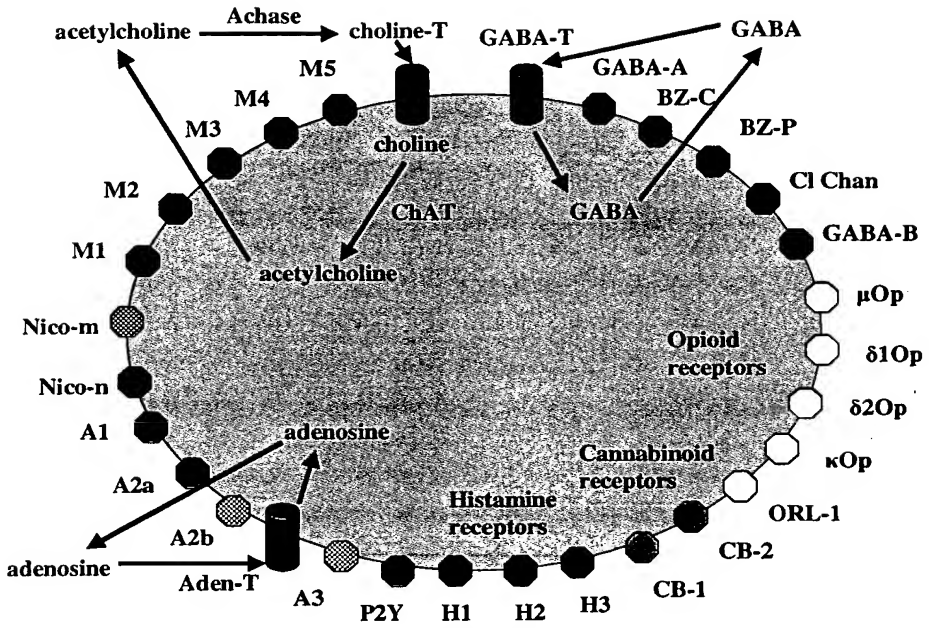

acetylcholine
Achase
choline-T
GABA-T
GABA
M5
GABA-A
M4
BZ-C
M3
choline
BZ-P
M2
Cl Chan
ChAT
GABA
M1
GABA-B
acetylcholine
μOp
Nico-m
Opioid
receptors
δ1Op
Nico-n
δ2Op
A1
adenosine
κOp
Cannabinoid
receptors
A2a
Histamine
receptors
ORL-1
A2b
CB-2
adenosine
Aden-T
A3
P2Y
H1
H2
H3
CB-1

FIG. 7

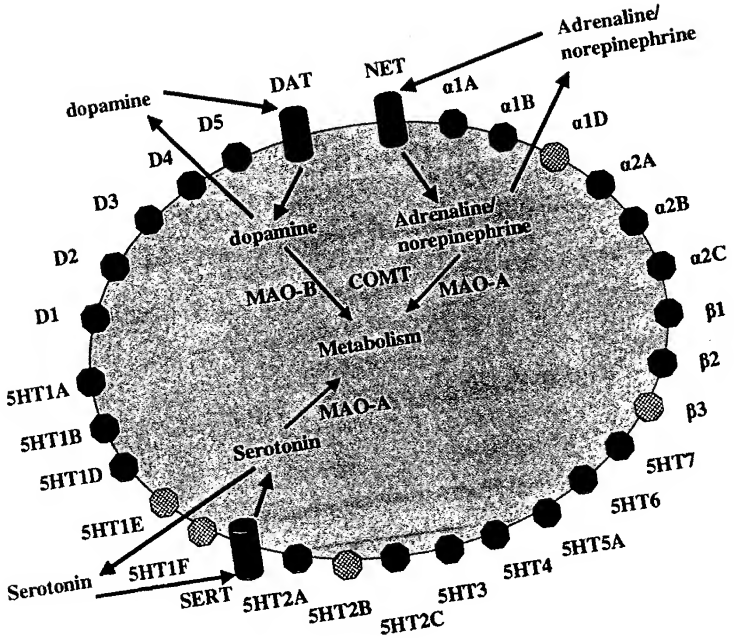

Adrenaline/
norepinephrine
dopamine
DAT
NET
α1A
α1B
α1D
α2A
α2B
α2C
β1
β2
β3
5HT7
5HT6
5HT5A
5HT4
5HT3
5HT2C
5HT2B
5HT2A
SERT
5HT1F
Serotonin
5HT1E
5HT1D
5HT1B
5HT1A
D1
D2
D3
D4
D5
dopamine
Adrenaline/
norepinephrine
MAO-B
COMT
MAO-A
Metabolism
MAO-A
Serotonin

FIG. 8

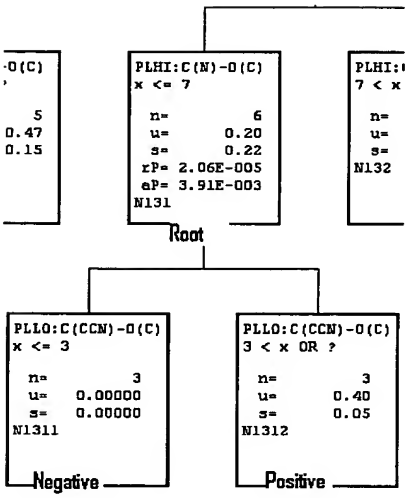

-O(C)
5
0.47
0.15
PLHI:C(N)-O(C)
x <= 7
n= 6
u= 0.20
s= 0.22
rP= 2.06E-005
aP= 3.91E-003
N131
PLHI:
7 < x
n=
u=
s=
N132
Root
PLLO:C(CCN)-O(C)
x <= 3
n= 3
u= 0.00000
s= 0.00000
N1311
Negative
PLLO:C(CCN)-O(C)
3 < x OR ?
n= 3
u= 0.40
s= 0.05
N1312
Positive

FIG. 9

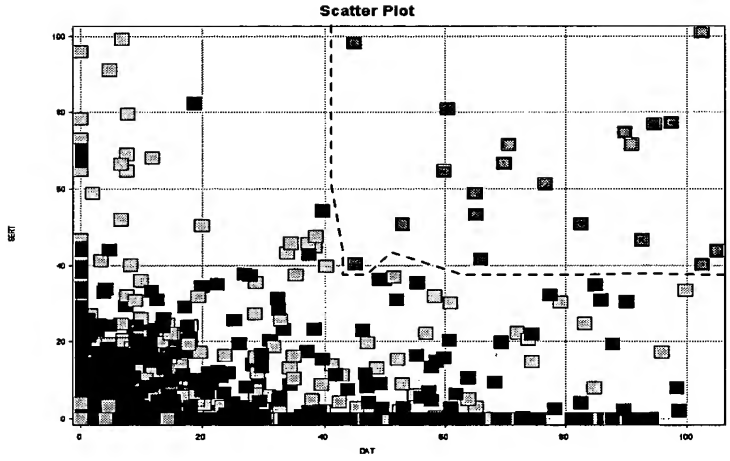


FIG. 10

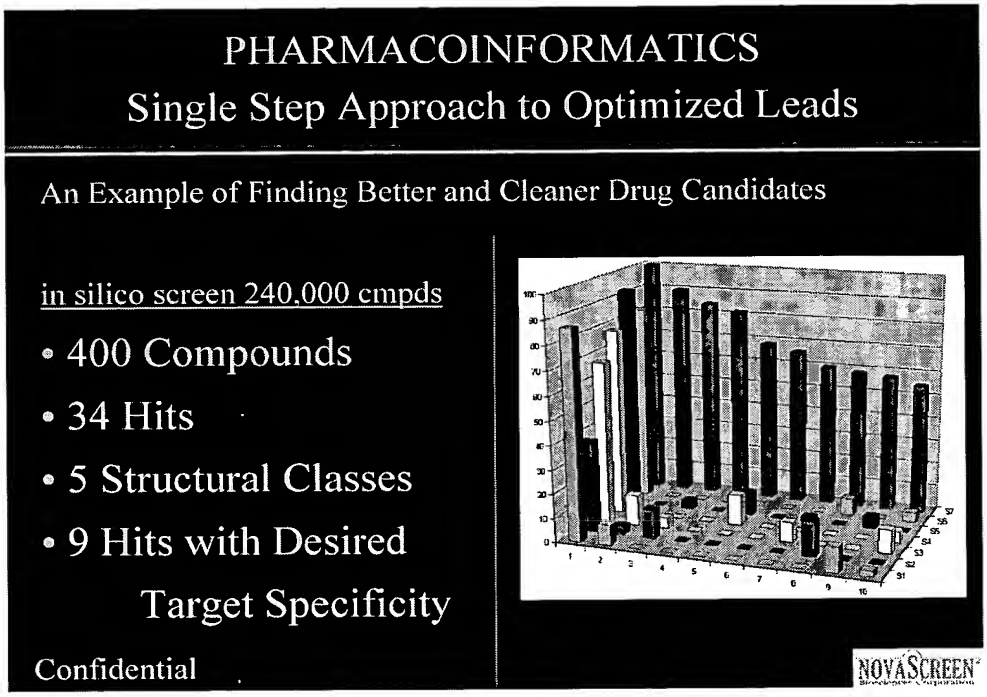

PHARMACOINFORMATICS
Single Step Approach to Optimized Leads
An Example of Finding Better and Cleaner Drug Candidates
in silico screen 240,000 cmpds
• 400 Compounds
• 34 Hits
• 5 Structural Classes
• 9 Hits with Desired Target Specificity
Confidential
NOVASCREEN

FIG. 11

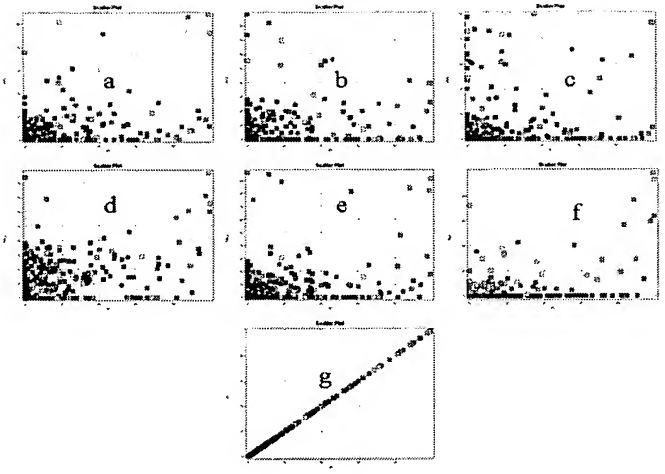


FIG. 12

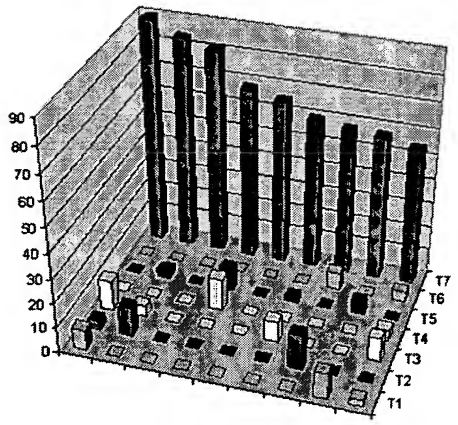


FIG. 13

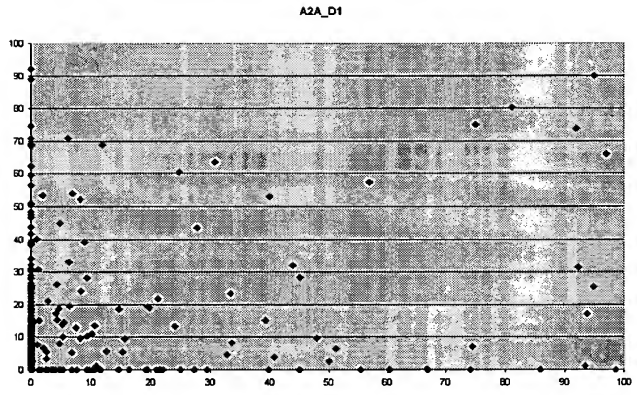


FIG. 14

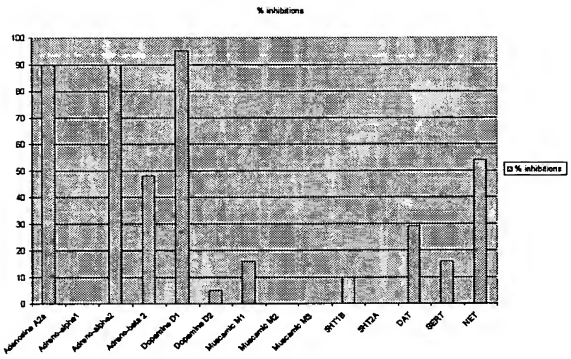

% inhibitions
100
90
80
70
60
50
40
30
20
10
0
% inhibitions
Adenosine A2a
Adrenoceptor alpha1
Adrenoceptor alpha2
Adrenoceptor beta1,2
Dopamine D1
Dopamine D2
Muscarinic M1
Muscarinic M2
Muscarinic M3
5HT1B
5HT2A
DAT
SERT
NET

FIG. 15

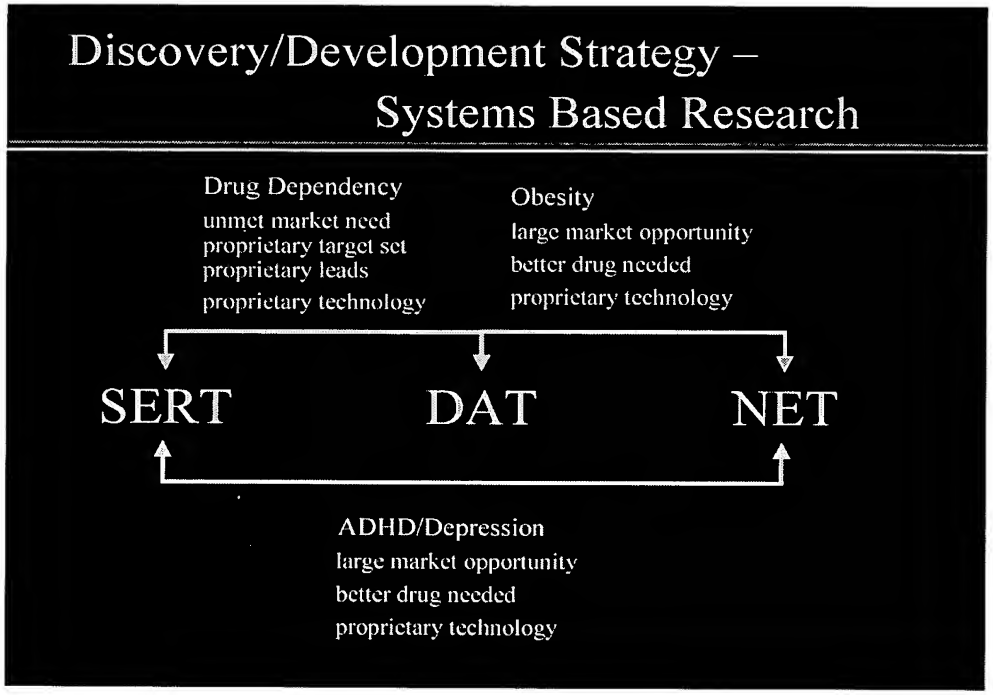

Discovery/Development Strategy –
Systems Based Research
Drug Dependency
unmet market need
proprietary target set
proprietary leads
proprietary technology
Obesity
large market opportunity
better drug needed
proprietary technology
SERT
DAT
NET
ADHD/Depression
large market opportunity
better drug needed
proprietary technology

FIG. 16

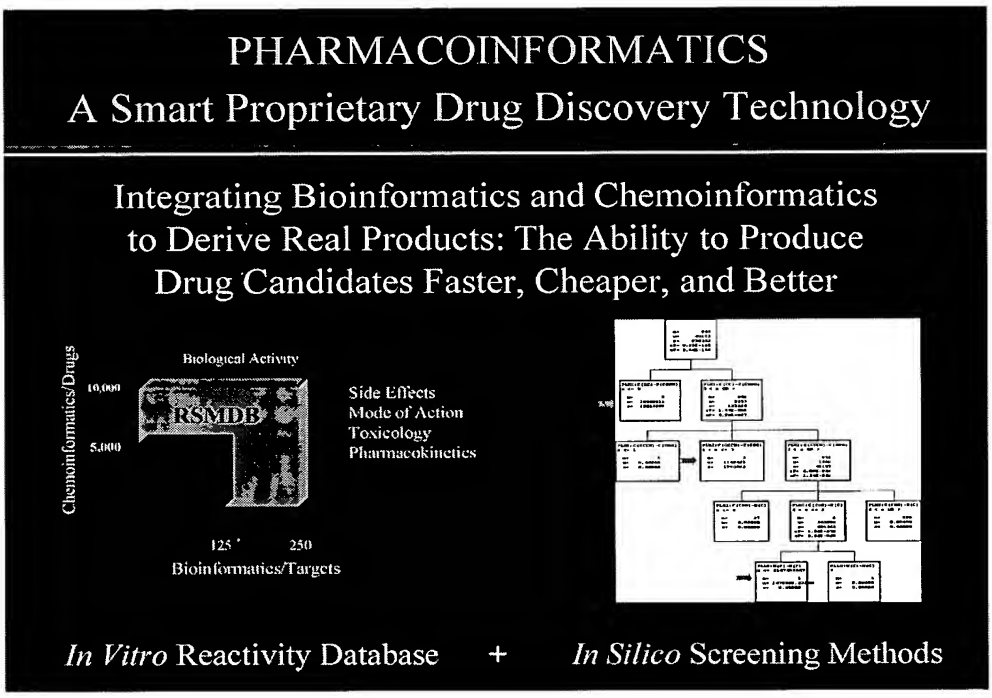

PHARMACOINFORMATICS
A Smart Proprietary Drug Discovery Technology
Integrating Bioinformatics and Chemoinformatics to Derive Real Products: The Ability to Produce Drug Candidates Faster, Cheaper, and Better
Biological Activity
Chemoinformatics/Drugs
10,000
5,000
RSMDB
125
250
Bioinformatics/Targets
Side Effects
Mode of Action
Toxicology
Pharmacokinetics
In Vitro Reactivity Database + In Silico Screening Methods

FIG. 17


RSMDB Content: Compound Classes
• Prescription Drugs (1500-2000)
• OTC Medicines; Veterinary Medicines
• Agricultural/Environmental Chemicals
• Drugs in Clinical Trials (& like structures)
• Discontinued/Failed Drug Candidates
(and like/similarity structures)
• Pharmacological Reference Agents
• Bioactive Natural Products
• + Structurally Diverse Chemical Compounds

FIG. 18


RSMDB Content: Target Classes
• Drug Discovery Molecular Targets
Receptors
Enzymes
Transporters
Ion Channels
Enriched set of market-validated GPCR targets, especially for CNS diseases
• Side Effect Targets
• In Vitro Toxicology Targets
• In Vitro Pharmacokinetic Targets
• Selected from 300 Available Developed Assays

FIG. 19


Pharmacoinformatics: Compressing
the Drug Discovery and Development Timeline
Drug Industry Standard: 10-12 Years to Market
10 Yrs
5 Yrs
0
Target
Library
Screen
Optimize
Preclinical
Clinical
NDA
RSMDB and *in silico* screening: one-step optimization
New uses of known safe compounds;
RSMDB focus on validated drug targets

FIG. 20

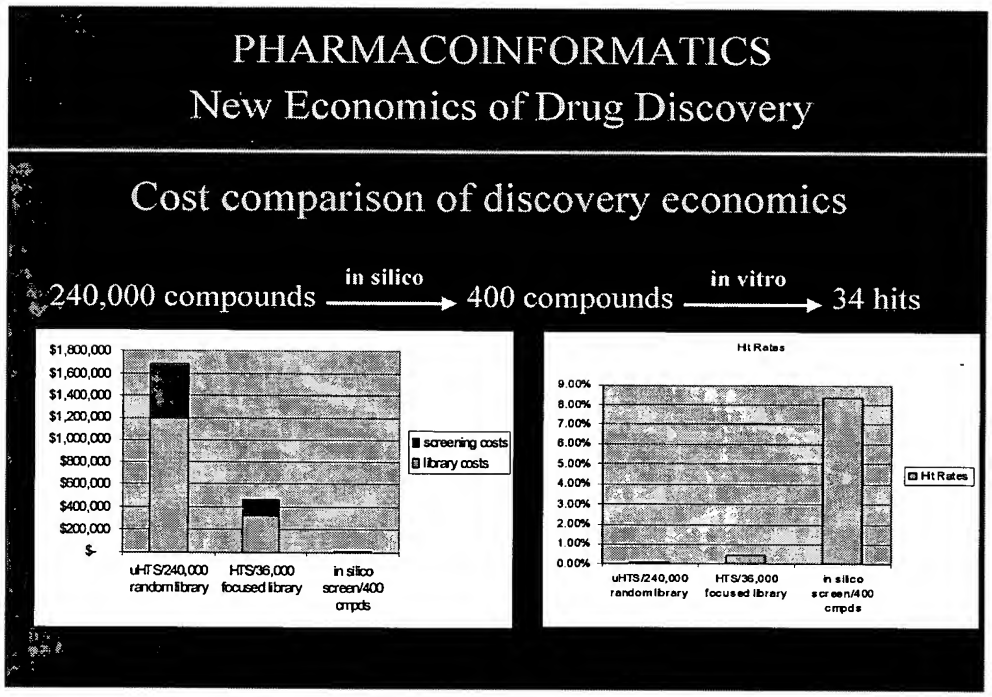

PHARMACOINFORMATICS
New Economics of Drug Discovery
Cost comparison of discovery economics
240,000 compounds
in silico
400 compounds
in vitro
34 hits
$1,800,000
$1,600,000
$1,400,000
$1,200,000
$1,000,000
$800,000
$600,000
$400,000
$200,000
$-
screening costs
library costs
uHTS/240,000 random library
HTS/36,000 focused library
in silico screen/400 cmpds
Hit Rates
9.00%
8.00%
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%
Hit Rates
uHTS/240,000 random library
HTS/36,000 focused library
in silico screen/400 cmpds

FIG. 21